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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/577,781 | 06/22/2006 | Masayoshi Yamaguchi | 4439-4042 | 9751 |

27123 7590 09/16/2008

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| EXAMINER | |
|---|---|
| LEAVITT, MARIA GOMEZ | |
| ART UNIT | PAPER NUMBER |
| 1633 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 09/16/2008 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/577,781 | YAMAGUCHI, MASAYOSHI | |
| | Examiner | Art Unit | |
| | MARIA LEAVITT | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,4 and 8-16* is/are pending in the application.

4a) Of the above claim(s) *4 and 8-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05-27-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

***Detailed Action***

Applicant is advised that the prior office action mailed on 09-02-2008 is vacated because the examiner inadvertently misscited one of the publications for the new rejection of claim 1 under 35 USC § 103.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 1, 4, 8-16 are pending. Claim 1 has been amended and claims 2 and 3 have been cancelled Applicant's amendment filed on 05-27-2008. Claims 4 and 8-16 were previously withdrawn from consideration pursuant to 37 CFR1.14 (b) as being drawn to nonelected invention, there being no allowable generic or linking claim and claims.
3. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.
4. Therefore, claim 1 is currently under examination to which the following grounds of rejection are applicable.

***Objections/ rejections withdrawn in response to Applicant arguments or amendments***

***Information Disclosure Statement***

The JP 07-123985 reference submitted by Applicants on 04-28-2006 with the IDS documents filed on 04-28-2006 was inadvertently not considered by the Examiner in the previous PTO-Form 1449 filed on 04-28-2006. In response to Applicant submission of file copies of the JP 07-123985 reference that was submitted previously with the IDS documents

filed on 04-28-2006, objection to IDS has been withdrawn. The JP 07-123985 reference has been reviewed and considered to the extent that the English abstract of the publication has been submitted as shown by the Examiner's initials next to the citation in the PTO-Form 1449 filed on 05-27-2008 attached hereto.

In addition the following references: JP 10-026623A, and JP 2003-164238 cited in the IDS filed on 04-28-2006, and JP 2002-177666 cited in the in the IDS filed on 07-11-2007 were previously considered to the extent that an English abstract of the publication was provided.

***Claim Rejections - 35 USC § 112- Second Paragraph***

In view of Applicants' cancellation of claims 2-3 and 5-7, rejection of claim 2-3 and 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language is rendered moot.

***Claim Rejections - 35 USC § 102(b)***

In view of Applicant's amendment of claim 1 to recite the limitation "rats of 36 to 50 weeks of age", rejection of claim 1 under 35 U.S.C. 102(a) as being anticipated by Yamaguchi et al. (Published on-line June 24, 2002; *J. Cell. Biochem* 86:520-529) has been withdrawn

Though Yamaguchi et al., discloses the generation of regucalcin transgenic rats with remarkable expression of regucalcin, Yamaguchi's disclosed rats were 5-6 weeks old and not 36 to 50 weeks of age.

***Rejections maintained in response to Applicant arguments or amendments:***

Claim 1 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

> a transgenic rat comprising in its genome a transgene comprising the rat regucalcin cDNA homozygously, wherein the transgenic rat overexpresses regucalcin, and shows at the stage of about 36 weeks to 50 weeks an increase in one or more of serum free fatty acid, triglyceride, HDL-cholesterol, free cholesterol and serum albumin,

does not reasonably provide enablement for claims directed to a transgenic, non-human animal that overexpresses regucalcin and is a model for hyperlipemia and/or hyperalbuminemia

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

***Response to Applicants' Arguments as they apply to rejection of Claim 1 under 35 USC § 112 – enablement.***

At page 7 of remarks, Applicants allege that claim 1 has been amended "to be directed to "a hyperlipemia and/or hyperalbuminemia rat model comprising a homozygote transgenic rat of 36 to 50 weeks of age into which a regucalcin gene is introduced and which overexpresses regucalcin." Support can be found throughout the specification and claims as filed, for example on pages 19-22 and claims 2 and 5 of the application as filed. Applicant respectfully directs the Examiner's attention to the current Office Action, where the Examiner admits: "[t]he specification discloses on page 19-22, the generation of a transgenic rat overexpressing regucalcin as a tool for to obtain fundamental knowledge of the onset mechanisms of hepatic diseases and hyperlipemia at the stage of advanced age" (see Office Action at page 5). Therefore,

it is believed that the rejection concerning enablement under 35 U.S.C. § 112, first paragraph has been overcome and, as such, applicant respectfully requests reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph rejection to claims 2-3 and 5-7". Such is not persuasive.

While applicants' arguments partially overcome some of the issues in relation to convey germline transmission of the transgene and the generation of a transgenic rat and not any transgenic non-human animal, some additional issues remain that are discussed below. A large embodiment of the instant application is to a transgenic rat model for a hyperlipemia and/or hyperalbuminemia comprising a homozygote rat of 36-50 weeks of age into which a regucalcin gene is introduced and overexpressed. Note that the instantly claimed homozygous rat model of 36-50 weeks does not exhibit a defined phenotype. As stated in the previous office action, the specification discloses the generation of a transgenic rat carrying the cDNA homozygously that were raised to 36 weeks of age (p. 20, [0032]) wherein serum concentrations of calcium, inorganic phosphorus, zinc, glucose, triglyceride, HDL-cholesterol, and albumin, according to the types of rats, transgenic rats (homozygotes) or wild-type rats, and to the sex were analyzed (p. 22, [0034]). In relation to serum components, results indicated age related changes for 14-, 25-, 36-, 50-week-old regucalcin transgenic rats. For example, serum lipid concentrations (e.g., free fatty acid, triglyceride, HDL-cholesterol, free cholesterol) was observed in female rats that were 14 weeks of age or older, and that the elevation was significant in 50-week-old (1-year-old) rats (p. 25, [0040]). Though the specification contemplates the use of the regucalcin transgenic rats in prevention or treatment of diseases associated with hyperlipemia and hyperalbuminea (p. 27, [0047]), the specification is silent about any correlation of a homozygote transgenic rat of 36 to 50 weeks of age overexpressing a regucalcin gene and a hyperlipemia and hyperalbuminea

condition. Additionally, no data or specific statistics are disclosed regarding the significance of overexpressing a regucalcin gene in a transgenic rat of 36 to 50 weeks of age with a hyperlipemia and hyperalbuminea disease. How does the instant transgenic rat model of 36 to 50 weeks of age truly represent the etiology of hyperlipemia and hyperalbuminea? Given that the specification and art do not disclose nexus between hyperlipemia and hyperalbuminea and over expression of regucalcin, an artisan would not know if the instant transgenic rat of 36 weeks to 50 weeks of age represents a model for hyperlipemia and hyperalbuminea. It is emphasized that specification only enables to a transgenic rat model at the stage of about 36 weeks to 50 weeks for a phenotype exhibiting an increase in one or more of serum free fatty acid, triglyceride, HDL-cholesterol, free cholesterol and serum albumin.

***Obviousness Type Double Patenting-No secondary Refence(s)***

Claim 1 remains rejected on the ground of nonstatutory double patenting over claims 1 and 2 of copending Application No. 10/804,515, now US. Patent 7, 355,093. Since Applicants did not provide a response to the merits of this rejection, claim 1 remains rejected for the reasons of record.

***New grounds of rejection***

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made

Claim 1 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi et al. (Published on-line June 24, 2002; *J. Cell. Biochem* 86:520-529 in view of Moravski et al., (*American Journal of Pathology*. 2003; pp:151-160). Yamaguchi et al., is considered proper prior art as the inventive entity of the Yamaguchi et al., reference is different from that of the instant application. The only shared inventor between the two is Masayoshi Yamaguchi.

Yamaguchi et al. teaches the generation of regucalcin transgenic rats with remarkable expression of regucalcin (Abstract). Moreover, Yamaguchi et al. discloses that a DNA fragment containing the regucalcin gene in pCXN2 was used for pronuclear microinjection of SD rat embryos to generate transgenic rats. The founder rats were mated to produce F1 liters. Male and female heterozygote rats were identified and bred to homozygosity (pg. 521, col. 2, paragraph 2). Yamaguchi et al. discloses that both 5-week-old homogeneous transgenic rats male and female showing prominent expression of regucalcin (p. 523, col. 2, paragraph 1) did not exhibit any significant difference in levels of triglyceride, free cholesterol and albumin (see Table I at page 528).

Yamaguchi et al. does not specifically teach transgenic rats of 36 to 50 weeks of age.

However, at the time the invention was made, Moravski et al., discloses that the transgenic Ren-2 rat, harboring the mouse Ren-2 gene, which is both hypertensive and exhibits enhanced extra-renal renin and angiotensin, were used to study endothelial cell proliferation in diabetes (pp. 151, col. 2, last paragraph; p. 152, col. 1 paragraphs 1 and 2). Moreover, Moravski et al., teaches that six-week-old Ren-2, spontaneously hypertensive, and Sprague-Dawley rats received either streptozotocin or control vehicle and were studied for up to 36 weeks (Abstract).

Results demonstrated that at 36 weeks, all diabetic rats had a lower body weight than their respective nondiabetic controls with other physiological parameters measured being the same at 8, 16, and 36 weeks (p. 154, col. 1, paragraph 2). Furthermore, Moravski et al., states, "These findings are consistent with the present study in which the spontaneously hypertensive rat (SHR) exhibited hypertension comparable to the Ren-2 rat, but did not display ocular endothelial cell proliferation even after 36 weeks of diabetes" (p. 157, col. 1, paragraph 2)

Therefore, in view of the benefits of generating transgenic rats with remarkable expression of regucalcin wherein at 5-week-old of age said homogeneous transgenic rats exhibit prominent expression of regucalcin with not significant difference in levels of triglyceride, free cholesterol and albumin, as taught by Yamaguchi et al.,., it would have been *prima facie* obvious for the skilled artisan at the time the invention was made, to optimized the these results by selecting other time- response weeks particularly, because Moravski et al., teaches transgenic rats expressing the mouse Ren-2 gene at different time points including 8, 16, and 36 weeks and over 36 weeks. There would have been a reasonable expectation of success in studying the 5-weeks transgenic rats of Yamaguchi et al., at 36 weeks of age or longer for the purpose of providing variations in the physiological responses induced by remarkable expression of regucalcin, since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 105 USPQ 233.

***Conclusion***

Claim 1 is rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is

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